REMARKS

Claims 1, 12, 23, 26, 38, 47-53, and 55-60 are pending. Claims 2-11, 13-22, 24-25, 27-37, 39-46, and 54 are canceled. Claims 57-60 are new. All claim amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Applicants are preparing English language translations of the Abstracts of JP 59-174567 and JP 63-218580, previously submitted in the IDS filed April 17, 2008.

Claims 57-60 are new and are supported by the specification. As alluded to in the office action, support for claims 57-59 is found throughout the present specification, for example, at p. 5, ll. 1-17. Claim 60 is supported throughout the specification and originally filed claims. Claims 57-60 are patentable over the cited references. Support for other claim amendments is found in the specification at p. 7 and at p. 22.

1. Applicants acknowledge and appreciate the courtesies extended by Examiner Prebilic during the interview that took place on June 6, 2008. Herewith, Applicants provide additional clarification, further supporting the patentability of the present claims.

2. Claims 1, 12, 23, 26, 38, 48, 50, 51, 53, 55 and 56 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement and because the specification allegedly does not enable one of ordinary skill in the art to which it pertains or with which it is most clearly connected to make the invention commensurate in scope with the claims. In regards to both the written description requirement and enablement, the PTO appears to object to the cited ranges within the rejected claims. Applicants respectfully traverse this rejection.

In compliance with the written description requirement and enablement requirement of 35 U.S.C. 112, first paragraph, the specification provides express, implicit, and/or inherent disclosure of the claimed ranges and discloses methods for forming and using the claimed compositions commensurate in scope with the recited ranges. The

specification provides enough specificity that one of ordinary skill in the art could make or use the claimed compositions without undue experimentation.

To satisfy the written description requirement, the patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention. (MPEP 2163(I)). With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. (MPEP 2163.05(III)). In the present application, one of ordinary skill in the ceramic arts would have considered the claim limitation of a ratio of "at least 50:50 alpha tricalcium phosphate:hydroxyapatite" or "at least 666:333" explicitly, implicitly or inherently disclosed in the originally filed specification. In particular, the application expressly recites ratios of 50:50, 666:333, 80:20 and 90:10, from which the person of ordinary skill in the art would reasonably conclude that the inventor had possession of the claimed range of at least 50:50.

Regarding enablement, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experiments. (MPEP 2164.01). The present specification provides a clear experimental procedure and teaches which variables to manipulate (e.g., sintering temperature) to produced compositions having the claimed ratios. The originally filed specification provides clear support for forming compositions of primarily and predominantly alpha tricalcium phosphate and clearly discloses how to make and use the claimed invention without undue experimentation. Accordingly, one of ordinary skill in the ceramic arts could easily follow the prescribed procedures of the present disclosure and form compositions commensurate in scope with the claimed ratios without undue experimentation.

More particularly, the originally filed specification discloses "converting an hydroxyapatite substance into primarily alpha tricalcium phosphate by sintering, and

providing stabilizing entities which stabilize and insolubilize the formed alpha tricalcium phosphate within the phosphate phases." (Specification, p. 6, ll. 26-29). In the specification, Applicants noted that at sintering temperatures of 1000°C, "the ratio was about 10:90 [hydroxyapatite:TCP] and at 1100°C the film was predominantly tricalcium phosphate...." (Specification, p. 5, ll. 7-11). Further, the present specification states that the conversion of hydroxyapatite phases "at sintering temperatures of over 1200°C is into primarily α-tricalcium phosphate with smaller amounts of some other phases also being formed." (Specification, p.12, ll. 9-12). As such, Applicants clearly describes high ratio (greater than 90:10 tricalcium phosphate:hydroxyapatite) compositions and clearly draws a nexus between sintering temperature and composition.

In addition to discussing the conversion of hydroxyapatite into primarily and predominantly alpha tricalcium phosphate, the specification also recognizes that a mixture of calcium phosphate phases has advantages. In particular, the specification recognizes that the presence of stabilizing entities "significantly and unexpectedly stabilizes the α-TCP within the calcium phosphate phases to provide a bioactive composition which supports and encourages the activity of both osteoblast and osteoclast." (Specification, p. 9, l. 29-p. 10, l. 2). It was found "that by providing a mixture of calcium phosphate phases which include hydroxyapatite and tricalcium phosphate, the degree of resorption is encouraged through a broad range where a film of predominantly α-tricalcium phosphate provides the highest degree of resorption, whereas a film of predominantly of hydroxyapatite provides a negligible degree of resorption." (Specification, p. 10, l. 28-p. 11, l. 3). Accordingly, the specification discloses a set of desired ratios and the sintering temperatures that provide such desired ratios. (See Specification, p. 12, l. 28-p. 13, l. 10). Throughout, the specification draws a clear correlation between the ratio of hydroxyapatite to tricalcium phosphate and the sintering temperature. As the sintering temperature increases, the specification clearly points out that the ratio of alpha tricalcium phosphate to hydroxyapatite also increases. As such, the specification not only explicitly discloses the formation of materials that predominantly include alpha tricalcium phosphate, but also provides a clearly enabled method for forming such materials, such as through the manipulation of sintering temperatures.

Further, the PTO has a high burden to provide evidence and reasons as to why one of ordinary skill in the art would not consider the inventor to have been in possession of the claimed invention at the time of filing and why the claims are not enabled. However, the Office Action merely states that the specification lacks support and that it was "unclear how to make the claimed invention at ratios exceeding 80:20 alpha tricalcium phosphate: hydroxyapatite, particularly ratios exceeding 90:10 alpha tricalcium phosphate: hydroxyapatite." Given the clear disclosure of ratios exceeding 90:10 and the correlation between sintering temperature and compositional ratio, the application does clearly teach how to make the claimed invention at ratios exceeding 90:10. Moreover, such statements do not appear to rise to the level of evidence and reasoning required in MPEP 2163 and 2164.

In addition, Applicants note that the PTO has recognized inherent disclosures in several patents that explicitly provide a range, but lack explicit disclosure of ranges defined by the phrase "at least" a value. For example, the PTO issued US 6,428,561, in which the claims read "at least 60% by weight of the total of the glue" and the specification only explicitly enumerates "up to 90%" and "from 60% to 90%." In another example, the PTO issued US 5,397,361, in which claim 12 enumerates "at least three minutes," while the specification only enumerates "approximately three minutes" or "a setting period of approximately three to five minutes." In a further example, the PTO issued US 5,603,338, in which the claims enumerate an etch rate of "at least 100 Angstroms per minute," while the specification enumerates the ranges 200-350 Angstroms per minute, 600 to 750 Angstroms per minute, 400 to 550 Angstroms per minute, and 100 to 250 Angstroms per minute. The present application likewise supports the claim element of "at least 50:50" and "at least 666:333," without the need for *in haec verba* recitation of the phrase.

For at least the foregoing reasons, claims 1, 12, 23, 26, 38, 48, 50, 51, 53, 55, and 56 comply with the requirements under 35 U.S.C. 112, first paragraph, including the written description requirement and enablement of the claimed ranges. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 112, first paragraph, rejections.

3. Claims 1, 12, 23, 26, 38, and 47 were rejected under 35 U.S.C. 102(b) as being anticipated by Ruys (article entitled "Silicon-Doped Hydroxyapatite") or, in the alternative under 35 U.S.C. 103(a) as obvious over Ruys. Applicants respectively traverse this rejection.

Present claim 1 is directed to a bioactive artificial sintered composition for supporting bone selectivity. The composition consists essentially of stabilized alpha tricalcium phosphate and hydroxyapatite at a ratio of at least 50:50 alpha tricalcium phosphate: hydroxyapatite. The stabilized alpha tricalcium phosphate is stabilized with a stabilizing entity selected from the group consisting of silicon entities, aluminum entities, barium entities, titanium entities, germanium entities, chromium entities, vanadium entities, niobium entities, boron entities, and mixtures thereof. The composition is bioactive to support osteoblast bone growth and to support extracellular resorption of the composition by osteoclasts. The composition is in the form of a powder, granules, or a bulk material.

Turning to the reference, Ruys presented work to determine the feasibility of chemically doping hydroxyapatite with silicon. At all silicon levels hydroxyapatite (HAp) formed and, at high silicon levels, α-tricalcium phosphate (α-TCP) and Si-P-O glass formed. (Ruys, Abstract). In particular, "both α- and β-TCP were formed, although β-TCP was favoured at low silicon levels and α-TCP was favoured at high silicon levels. Further, at higher silicon concentrations, a broad X-ray diffraction peak with a *d* spacing of 0.16-0.26 nm formed. Since both silicon and phosphorous are oxide glass formers, this peak is a result of the presence of a Si-P-O glass. For progressively higher silicon levels, the glass became the dominant phase. At very high dopant levels, approximate area ratios of the main diffraction peaks of HAp and TCP suggested that the TCP content was slightly greater than the HAp content." (Ruys, page 77, paragraph 3). As such, Ruys discloses that at high silicon levels the TCP content was slightly greater than hydroxyapatite content, but the Si-P-O glass phase was the dominant phase.

High levels of Si-P-O glass and in particular, high levels of silicon outside of the crystal matrix of the calcium phosphate species hinder the bioactivity of the material. As described in the Declaration by Dr. Smith dated November 2, 2007, high levels of silicon

produce a material that limits initial cell attachment to the surface. In addition, a cited impartial third party reference clearly states that high levels of silicon inhibit osteoclast activity. (See Best et al. pg. 986). Thus, high levels of silicon, which, as taught by Ruys, leads to the formation of Si-P-O glass as a dominant phase, materially affects the bioactivity of the material in that it inhibits osteoclast activity.

With regard to claim 1, Applicants have used the transitional phrase "consisting essentially of," which limits the scope of a claim to only those the specific materials or steps that do not materially affect the basic and novel characteristics of the claimed invention, herein bioactivity. Clearly, the compositions disclosed by Ruys have a predominant phase of Si-P-O glass for any embodiment having notable α-TCP content, which would materially affect the basic and novel characteristics of the claimed invention, namely bioactivity, including osteoclast activity. The PTO has cited MPEP 2111.03, which is instructive on issues relating to interpretation of "consisting essentially of" language. That section makes it clear that Applicants have the burden to establish the identity of basic and novel characteristics; otherwise "consisting essentially of" shall be construed by the PTO to be "comprising." In particular, Applicants are to provide a clear indication in the specification or claims of what the basic and novel characteristics actually are and are to show that the introduction of additional components would materially change the characteristics of Applicant's invention. (MPEP 2111.03).

Applicants have met this burden by (i) clearly indicating and defining the basic and novel characteristics in the specification, (ii) expressly reciting in the claims one of the basic and novel characteristics (i.e., the composition is bioactive), and (ii) providing impartial third party evidence that high silicon content, which Ruys states leads to a predominant glass phase, hinders bioactivity (i.e., see Best et al., pg. 986). Interestingly, the MPEP chose to cite *In re Janakirama-Rao* (137 USPQ 893, 895-96 (CCPA 1963)) involving facts similar to those at hand, in which excessive silicon content was precluded by consisting essentially of language, based on evidence of deleterious affects of silicone content greater than 0.5 wt%.

In the specification, Applicants clearly indicate what is considered to be a basic and novel characteristic of the invention by stating that it "has now been found that the presence of stabilizing entities significantly and unexpectantly stabilized the α-TCP within the calcium phosphate phases to provide a bioactive composition which supports and encourages the activity of both osteoblasts and osteoclasts." (Specification, p. 9, l. 28 – p. 10, l. 12). In addition, Applicants provided a definition of bioactive, which includes controlled extracellular resorption of the composition by osteoclasts. (Specification, p. 10, ll. 10-15). Applicants further discuss how such resorption is controlled by the ratios of α-tricalcium phosphate to hydroxyapatite. (Specification, p. 10, l. 28 – p. 11, l. 3). As such, the specification provides a clear indication of the basic and novel characteristic, bioactivity. In addition, Applicants further claimed the bioactivity in both independent claims 1 and 55, going over and above the minimum burden placed on Applicants to indicate the basic and novel characteristic.

In response to Applicants' previous remarks, the PTO acknowledges Applicants' assertion that "consisting essentially of" precludes SI-P-O glass as disclosed as present in Ruys. However, the PTO concludes that "consisting essentially of" does not preclude other calcium phosphate phases or other contaminants. In fact, the language "consisting essentially of" precludes any component that would materially affect the basic and novel characteristic of the composition. Further, the statement in the specification at page 12 that the contaminant "preferably does not affect the composition and morphology of the stabilized composition in any manner which will affect the support of bone cell activity thereon," referenced by the PTO, further emphasizes the Applicants' point that various contaminants, including SI-P-O glass and other contaminants, have an adverse influence on bone cell activity, the relied upon basic and novel characteristic. Given its proper weight, the statement that the contaminant "preferably does not affect the composition and morphology of the stabilized composition in any manner which will affect the support of bone cell activity thereon," provides a clear nexus between the composition and the basic and novel characteristic, bioactivity, as required for the interpretation of the "consisting essentially of" transitional phrase. Furthermore, Applicants provided an impartial third party reference that clearly states that high levels of silicon inhibit osteoclast activity. (See Best et al. pg. 986).

Accordingly, Applicants have provided a clear indication of the basic and novel characteristics, not only in the specification, but also in the claims. Further, Applications have provided evidence that introduction of additional components would materially change the characteristics of the invention.

Turning to the cited reference, the Ruys material does not *consist essentially of* a bioactive, high α-TCP content material since the high α-TCP-content materials of Ruys contain notable Si-P-O glass, significantly compromising the bioactivity of the material in terms of osteoclast activity. In this regard and as noted in the Declaration by Dr. Smith dated November 2, 2007, Applicants have found that external Si-containing phases, such as Si-P-O glass, in amounts greater than 20 wt% compromise bioactivity as claimed, that is, "to support osteoblastic bone growth and to support extracellular resorption of said composition by osteoclasts."

In contrast to Ruys, Applicants have discovered a method for producing bone replacement compositions predominantly formed of stabilized calcium phosphate phases without the formation of a significant amount of silicon compounds outside of the calcium phosphate matrices. As noted in the Declaration, the method is significantly different from the method disclosed in Ruys, and the material produced by such a method is different from the material disclosed by Ruys. In particular, the compositions produced by the methods discovered by Applicants are predominantly calcium phosphate compositions and have less than 5 wt% of phases including silicon compounds other than silicon stabilized calcium phosphate compositions, such as less than about 3 wt% silicon compound phases. As further explained in the Declaration, the absence of a significant amount of silicon compositions other than the silicon stabilized calcium phosphate compounds in the presence of stabilized α-TCP permits bioactivity and, in particular, permits balanced osteoblast and osteoclast activity as claimed.

Accordingly, based on the transitional phrase "consisting essentially of," claim 1 clearly precludes the presence of Si-P-O glass in amounts over 20 wt%, and certainly as a "predominant phase" as taught by Ruys. As such, Ruys fails to anticipate claim 1 and

claim 1 is not obvious over Ruys because the high TCP content materials of Ruys include Si-P-O glass as a predominant phase.

With respect to claim 12, Applicants have presented evidence above and in previous responses that Ruys fails to inherently disclose the claimed features.

Alternatively, the PTO posits that it would have been obvious to make higher dopant materials that would fall within the claimed range when a more biodegradable material was desired. However, Ruys clearly does not enable such a composition having the claimed bioactivity since the composition of Ruys that has slightly greater α-tricalcium phosphate than hydroxyapatite also is predominantly Si-P-O glass. Applicants have provided a clear explanation as to how such Si-P-O glass content materially affects the recited bioactivity.

Further, the PTO appears to misinterpret the conversion reactions disclosed in the specification. Applicants postulated that in one mechanism, 2 mols of hydroxyapatite are converted to 3 mols of tricalcium phosphate and 1 mole of CaO. (Specification, p. 13, l. 14). Applicants further suggest than one mole of CaO can be reacted with 1 mol of SiO_2 to form 1 mol of $CaSiO_3$. Applicants note that a stoichiometrically complete reaction uses 1 mol SiO_2 per mol CaO. However other ratios can be used. (Specification, p. 14, ll. 11-14). Accordingly, a composition that converts hydroxyapatite to tricalcium phosphate in ratios of 80:20, may produce some amount of CaO that can be reacted with up to an equal molar amount of SiO_2. In contrast to the assertions by the PTO that such a composition would have 40% silica, the amounts of silica added to the reaction, even if the reaction were to stoichiometric completion, would be less than 5 wt%. Note the PTO appears to be performing the calculation using an incorrect mol% calculation that ignores the presence of tricalcium phosphate and CaO.

For at least the foregoing reasons, claims 1, 12, 23, 26, 38, and 47 are not anticipated or rendered obvious by Ruys. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 103(a) rejection.

4. Claims 1, 12, 38, 46-53, 55, and 56 were rejected under 35 U.S.C. 102(b) as being anticipated by Davies (WO 94/026,872). Applicants respectfully traverse this rejection.

Davies is directed to the formation of thin film calcium phosphate materials overlying quartz substrates. The thin films are formed through the deposition of hydroxyapatite (not doped with silicon) over a quartz substrate followed by sintering. (Davies, p. 6, ll. 23-37). Davies does not disclose the formation of a stabilized sintered powder, granules, or bulk material. In contrast, the present claims are directed to compositions that take the form of powders, granules, or bulk materials.

For at least the foregoing reasons, claims 1, 12, 38, 47-53, 55, and 56 are not anticipated by Davies. As such, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. 102(b) rejection.

Applicant(s) respectfully submit that the present application is now in condition for allowance. Accordingly, the Examiner is requested to issue a Notice of Allowance for all pending claims. Should the Examiner deem that any further action by the Applicants would be desirable for placing this application in even better condition for issue, the Examiner is requested to telephone Applicants' undersigned representative at the number listed below. The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-3797.

Respectfully submitted,

Date

John R. Schell, Reg. No. 50,776
Agent for Applicant(s)
LARSON NEWMAN ABEL &
POLANSKY, LLP
5914 West Courtyard Drive, Suite 200
Austin, TX 78730
(512) 439-7100 (phone)
(512) 439-7199 (fax)